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REVIEW ARTICLE

Daylight-mediated photodynamic therapy for actinic damage in Latin America: consensus recommendations†

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SUMMARY

Although conventional photodynamic therapy (c-PDT) using methyl aminolevulinate cream (MAL) is effective for the treatment of grade I-II facial and scalp actinic keratosis (AK), it is associated with treatment-related pain for some patients. Daylight-mediated PDT (DL-PDT) has shown similar efficacy to c-PDT, was nearly painless, and was well tolerated. Overall, DL-PDT effectively treats AK and offers a simpler and better tolerated treatment option than c-PDT. This consensus panel provided recommendations on the use of DL-PDT in Latin America (LATAM) for the treatment of actinic damage associated with few or multiple AKs. The panel was comprised of eight dermatologists from different LATAM countries who have experience using PDT for the treatment of actinic damage. The panel reviewed the relevant literature and provided personal expertise with regard to using DL-PDT for the treatment of photodamage with or without AK. The recommendations formulated by the expert panel provide evidence-based guidelines on all aspects of DL-PDT for the treatment of actinic damage associated with AK in different regions of LATAM. These recommendations provide guidance for dermatologists to ensure maintenance of efficacy and safety of DL-PDT when treating actinic damage, associated with few or multiple AKs in sun-exposed skin.

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†The recommendations set forth in this article are provided for dermatologists and all practitioners treating cutaneous malignancies and reflect the best data available including publications and the experts' own experience, at the time this report was published. The results of future studies may lead to alteration of the conclusions or recommendations of this publication. It may be necessary to modify these recommendations in the interest of specific patients or under special circumstances. Just as adherence to these recommendations may not constitute a defense against a claim of negligence, deviation from them should not necessarily be deemed negligent. Indications of photodynamic therapy with methyl aminolevulinate vary according to individual country approvals and daylight-mediated photodynamic therapy is not yet approved in all Latin America countries. Therefore, the consensus recommendations described herein may not apply to all countries.

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The incidence of non-melanoma skin cancers (NMSCs), including actinic keratosis (AK), is rising worldwide (1). Prevalence ranges from 13% to 15% in Brazil (2) and England (3) to 60% in Australia (4). The highest incidence is observed in populations who live near the equator (5). NMSCs and AKs are also among the first nine causes of dermatological consultation in Medellin, Colombia (6). Despite this high prevalence, clinical diagnosis and knowledge regarding the condition in the general public is low. AKs are pre-cancerous lesions with risk to develop into invasive squamous cell carcinoma (7, 8); hence, a quick and effective treatment is required (9). AK is a chronic disease arising on skin with actinic damage, requiring regular treatments as well as regular follow-up. There are different treatment options available including cryotherapy, topical, and photodynamic therapy (PDT).

Conventional PDT (c-PDT) using methyl aminolevulinate cream (MAL) (Metvix®; Galderma, Lausanne, Switzerland) under a 3-h occlusion prior to illumination using a light-emitting diode (LED) lamp has been used to treat grade I-II facial and scalp AK, with good efficacy and cosmesis (10, 11). However, use of c-PDT is affected by the following limitations: (i) the area to be treated is restricted by the size of the LED lamp; (ii) treatment may be painful for some patients, especially those with facial and scalp AK on large fields, and (iii) the procedure requires specific illumination equipment (Aktilite® CL 128; Photocure ASA, Oslo, Norway).

Use of daylight-mediated PDT (DL-PDT) for AK is supported by evidence from five clinical studies. DL-PDT showed similar efficacy to c-PDT in the treatment of facial and scalp AK, was nearly painless, and was well tolerated (12–17). In addition, use of daylight overcomes the requirement for illumination equipment. The rationale to use DL-PDT (without the need for ultraviolet [UV] exposure) is that protoporphyrin IX (PpIX) is activated by different wavelengths within the visible light spectrum.

LITERATURE REVIEW

Efficacy

Different lesion response rates from four of five DL-PDT randomized studies are compared (Table 1). One study directly compared DL-PDT and c-PDT for the treatment of AK (12). This intra-individual design study involving 29 patients showed similar efficacy between DL-PDT and c-PDT. Despite this, much less pain was reported for DL-PDT compared to c-PDT. These findings (similar efficacy and minimal pain) were corroborated by two DL-PDT studies using various concentrations of MAL cream and durations of daylight exposure (2 h vs. 3 h) (13–15).

A recent phase III, 24-week, intra-individual design study comparing DL-PDT to c-PDT was conducted in Australia (16). A total of 100 patients with facial/scalp AKs were treated with DL-PDT and c-PDT on either side. Twelve weeks following a single treatment session, DL-PDT was non-inferior to c-PDT in lesion complete response rate (percentage reduction of 89.2% vs. 92.8%, respectively; 95% confidence interval [CI] [−6.8; −0.3]; per-protocol [PP] population). This was corroborated by the intent-to-treat (ITT) analysis (86.4% vs. 89.9%, respectively; 95% CI [−6.6; −0.4]). At study end, complete response was sustained in 96% of lesions regardless of treatment (16). Finally, patient satisfaction was significantly better with a higher motivation for a future treatment with DL-PDT compared to c-PDT (16).

A DL-PDT study was recently conducted in Western Europe. Preliminary results confirmed the findings of the Australian DL-PDT study, with similar efficacy observed between DL-PDT and c-PDT, and almost no patient-reported pain with DL-PDT (17).

Table 1. Lesion response rate and daylight exposure data*

Study	*N*	Lesion response rate (%) Mean ± SD	Exposure time (min) Mean ± SD
Wiegell *et al.* (12)	29	79.0 ± 17.5	150 ± 12
Wiegell *et al.* (13)	29	78.2 ± 19.5	244 ± 89
Wiegell *et al.* (14)			
All patients	120	76.5 ± 26.2	160 ± 53
1½-h exposure	58	77.2 ± 23.3	131 ± 37
2½-h exposure	62	74.6 ± 27.3	187 ± 52
Rubel (16)	100	89.2 ± 15.0	121 ± 5

*From 3 Scandinavian and 1 Australian studies.

A recent open-label study conducted in Brazil, including 14 patients with multiple grade I-II facial AKs, assessed the efficacy and tolerability of DL-PDT (18). These patients received one ($N = 10$), two ($N = 3$), or three ($N = 1$) sessions of DL-PDT at 1-month intervals. The study included a 3-month follow-up after the last session. Lesion response rate was 86% for all patients, and 87.9% for the 10 patients who underwent a single session.

Safety

In the three Scandinavian studies, DL-PDT was almost painless (Table 2). In the first study (12), some erythema was observed following DL-PDT, probably caused by sunburn due to the absence of sunscreen application on the treated area. In the second study (13), a chemical sunscreen was applied to all areas exposed to the sun. The incidence of erythema was not different between 8% and 16% MAL cream (13). Of note, use of a chemical sunscreen has no effect on the efficacy of the treatment as it does not prevent visible light from penetrating into the skin and activating PpIX.

It was also shown that continuous exposure to daylight (within 30 min following application of 16% MAL cream) was recommended to avoid accumulation of PpIX and further pain.

In the third study (14), most patients reported erythema after treatment. However, the incidence of erythema between the 2-h and 3-h exposure groups was not different. In addition, treatment efficacy was not different between the two groups.

The Australian phase III study demonstrated that DL-PDT was nearly painless, with significantly lower pain for DL-PDT vs. c-PDT (Table 2). Moreover, DL-PDT was better tolerated compared to c-PDT (16). The same benefits in terms of local safety with DL-PDT have been observed in the recent European phase III trial (17).

In the recent Brazilian study, the mean pain score reported was 2 (visual analog scale 0–10). The patients considered DL-PDT to be a painless method. Patients who had previously undergone c-PDT treatment reported that DL-PDT was better tolerated (18).

Efficacy/dose relationship

The results of the second and third Scandinavian studies (13, 14) showed that light dose was associated with lesion response rate ($P = 0.005$, $R^2 = 0.27$) only in a small subset of patients (3/29) who received less than 8 J/cm^2. However, this association was not reported in the Australian and Brazilian studies (16, 18).

According to the results of the third Scandinavian study, a 2-h exposure to daylight, ending 2.5 h after MAL application, is considered sufficient to effectively treat AK (14). This was confirmed by the Australian and European phase III studies as well as the more recent Brazilian study (16–18).

Of note, the third Scandinavian study (14) concluded that DL-PDT efficacy is not affected by weather conditions, and data from a very recent meteorological study suggest that DL-PDT can be performed throughout the year in Latin America (LATAM) (19).

USE OF DL-PDT IN LATAM: CONSENSUS RECOMMENDATIONS

These consensus recommendations formulated by the DL-PDT expert panel, comprised of eight dermatologists from LATAM countries, aimed to provide evidence-based guidelines on all aspects regarding DL-PDT.

Patient selection

The experts recommend DL-PDT to be used as a favorable alternative to c-PDT for the treatment of patients with actinic damage associated with few or multiple grade

Table 2. Patient-reported post-treatment pain

Study	DL-PDT Pain Score* Mean ± SD	c-PDT Pain Score* Mean ± SD	*P*-value
Wiegell *et al.* (12)	2.0 ± 1.9	6.7 ± 2.2	$P < 0.0001$
Wiegell *et al.* (13)	2.0 ± 1.7	–	–
Wiegell *et al.* (14)	1.3 ± 1.5 (average of 1.5 and 2.5 h treatments)	–	–
Rubel *et al.* (16)	0.8 ± 1.2	5.7 ± 2.3	$P < 0.001$

*Mean maximal pain score based on a numerical rating scale from 0 (no pain) to 10 (extreme pain).

I-II facial and scalp AKs. The objective of DL-PDT is to treat AK as well as field actinic damage (subclinical lesions), thus preventing new lesion occurrence (20, 21). AK is a recurring condition, and therefore, several treatment sessions may be required in the long term.

Treatment

DL-PDT is a medical procedure that should be performed by a dermatologist

DL-PDT must be performed by a trained dermatologist. The procedure is not dependent on weather conditions (except rain) and can be used if the weather and temperature permit the patient to remain exposed to daylight for 2 h. In LATAM, DL-PDT can be performed throughout the year (19). The procedure protocol is summarized (Table 3) and treatment results with DL-PDT are illustrated (Fig. 1).

Skin preparation

Preparation of the skin is an important step of the treatment. Removal of scales and crusts augments penetration of 16% MAL cream. Skin preparation is carried out in the dermatologist's clinic. Several methods are available such as surface curettage (22), slightly abrasive pads or microdermabrasion. Lasers and microneedling (up to 500 μm) may be used with caution using smooth parameters (for drug delivery enhancement) to avoid excessive phototoxic reaction, thus allowing to treat subclinical lesions and improve the cosmetic outcome. All areas with actinic damage should be prepared, including each AK, before MAL application (23).

Experts do not recommend the treatment of grade III (hyperkeratotic) AK with DL-PDT. For patients with hyperkeratotic lesions, pretreatment with salicylic acid or urea prior to PDT can be performed (24).

Table 3. DL-PDT with 16% MAL cream—Protocol

Who?
Treatment of actinic damage associated with few to multiple grade I-II AKs in areas easily exposed to daylight
When?
Throughout the year in LATAM. All weather conditions except rain and uncomfortable temperatures
How?
Wash the skin
Apply a chemical sunscreen (without any physical filter such as titanium dioxide, zinc oxide, or iron oxide)
Prepare the skin by removing scales and crusts and roughen the surface of the skin to enhance 16% MAL cream penetration. Alternatively, skin preparation can be done before sunscreen application
Apply a thin layer of 16% MAL cream (without occlusion)
Expose to daylight nearby the clinic At the latest within 30 min Continuously for 2 h
Patient must return to the clinic after the 2-h exposure, to wash off the 16% MAL cream, re-apply sunscreen, and receive post-procedure instructions. Then, the patient must return home and stay indoors for the rest of the day
Evaluate lesion response as per usual follow-up

Sunscreen

Sunscreen (sun protection factor ≥30) is necessary to protect against UV radiation during daylight exposure (22). Use of chemical sunscreen instead of physical sunscreens ensures that the skin is exposed to visible light which is required for the activation of PpIX. Sunscreens using physical filters (zinc oxide, titanium dioxide, or iron oxide) are to be avoided.

Data have shown that there is no interaction between 16% MAL cream and chemical sunscreen (25). Chemical sunscreen can be applied before or after skin preparation (22, 26) and always before application of 16% MAL cream.

Sunscreen must be applied on treated areas as well as on all areas exposed to the sun. Sunscreen application must be carried out in the dermatologist's clinic to monitor the procedure, and ensure an appropriate chemical sunscreen is used along with the recommended quantity (2 mg/cm^2).

MAL application

It is recommended that 16% MAL cream is applied, using gloves or a spatula, on the entire face, with a larger quantity of cream applied on the AK lesions (18). For treatment of the full face, a quantity of approximately 1–2 g is considered sufficient. Occlusion is not necessary after application of 16% MAL cream. Indeed, similar fluorescence has been observed whether 1 mm 16% MAL cream thickness was applied, or 0.5 mm, 0.2 mm, and 0.1 mm (27).

Daylight exposure

Daylight exposure can be performed at any time, during the morning or afternoon. It is recommended that the

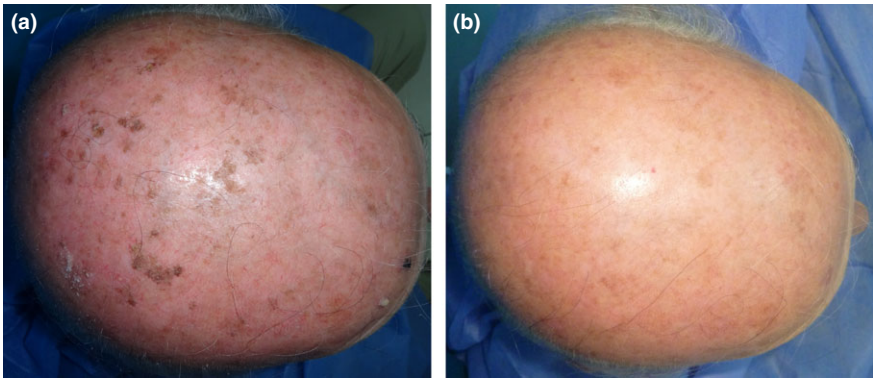

Fig. 1. Treatment area before (a) and after (b) DL-PDT*. *Photographs are courtesy of Dr Gaston Galimberti.

patients are exposed to daylight in the vicinity of the clinic to ensure timely return after 2 h. Daylight exposure must commence immediately after application of 16% MAL cream or within 30 min after the application. Delayed exposure to daylight leads to PpIX accumulation in the cells and consequently increases the risk of treatment pain.

Two hours of uninterrupted daylight exposure are required to produce and activate sufficient PpIX. Shorter daylight exposure leads to inadequate PpIX synthesis and consequently decreased efficacy. However, patients may seek shade intermittently if temperatures during exposure become uncomfortable. Longer daylight exposure is not associated with increased efficacy and may aggravate treatment-related erythema (15).

There is no need to monitor the light dose as there was no relationship between efficacy and irradiance or weather in the DL-PDT clinical studies despite large variations in irradiance (13, 14, 16, 18).

Post-exposure recommendations

Following the 2 h of daylight exposure, it is recommended that patients return to the clinic for observation, removal of 16% MAL cream, and reapplication of sunscreen. Patients should return home and stay indoors for the rest of the day. The patients should be protected from the sun for the next 48 h. Use of a gentle cleanser and moisturizer as post-procedure care for a week following DL-PDT is recommended to avoid crusting and minimize downtime.

Follow-up

Assessment of the clinical response should be performed 1 to 3 months after DL-PDT depending on the treating physician. For more severe disease, a closer follow-up at 1 month is recommended whereas for less severe disease a follow-up at 3 months is sufficient.

Communication with patients regarding DL-PDT

- Chronic exposure to UV radiation is responsible for the development of AK. DL-PDT requires visible light for the treatment. An appropriate sunscreen protects against UV radiation during daylight exposure, while allowing visible light to activate the treatment. This is important to explain to patients already sensitized to the dangers of UV radiation.
- DL-PDT is an efficacious, tolerable, and simple procedure, for the treatment of actinic damage associated with AK.
- Patients must be informed about the potential risk for adverse reactions such as erythema and scabbing. These transient adverse reactions resolve spontaneously within a week after DL-PDT.
- Skin preparation for treatment (thinning of the stratum corneum) is necessary to enhance absorption of 16% MAL cream. Use of chemical UV filters or protectors is recommended before or after thinning of the stratum corneum. Application of the cream to the treatment area should be homogeneous.
- Patients must be exposed to daylight within 30 min after application of 16% MAL cream, and must remain exposed to daylight continuously for 2 h before returning to the clinic 2.5 h after MAL application. It is recommended that patients are not exposed to daylight after DL-PDT is completed.
- The experts recommend that a second session of DL-PDT can be performed between the 4 weeks and 3 months re-evaluation in case of non-responsive or new AK lesions.

Instructions for the patient

1. Before coming to the clinic for the procedure, do not apply makeup on the area to be treated. After the procedure, the experts' recommendations are:
2. Expose treated area to daylight continuously for 2 h, but not necessarily under direct sun exposure.
3. Return to the clinic to complete the treatment with a thorough face wash.
4. Patient should not expose further the treated area to sunlight on the day of treatment. Physical sunscreens may be used to protect the treated area (28).
5. Apply sun protector during the day and moisturizing lotion at night for 5 days following treatment.
6. Avoid the use of cosmetics, abrasive substances, and strong soaps on the treated areas for 5 days following treatment.
7. In case of pain, burning sensation or any other sign of intense inflammation, contact your dermatologist immediately.

CONCLUSIONS

These evidence-based consensus recommendations provide a set of guidelines for dermatologists in LATAM treating AK with DL-PDT. DL-PDT offers similar efficacy, improved tolerability, reduced in-clinic treatment times, and little or no pain compared to c-PDT, as well as the ability to treat large areas of actinic damage. Hence, DL-PDT with 16% MAL cream can be included as an effective procedure for the treatment of patients with few to multiple facial and scalp grade I-II AKs.

CONFLICTS OF INTEREST

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